Although no fees are believed to be due at this time, please charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: February 13, 2002

By: _____

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Version with markings to show changes made

In the Specification:

Paragraph [0001] has been amended as follows:

- - This application [is a continuation-in-part and] claims priority under 35 U.S.C. § 1.19(e) of U.S. Provisional Application No. 60/252,294 filed on November 21, 2000 and U.S. Provisional Application No. 60/310,725 filed on August 7, 2001. - -

Paragraph [0024] has been amended as follows:

- - Figure 2 is a schematic illustration of the static extended tethering approach. In the first step, a target molecule containing or modified to contain a free thiol group (such as a cysteine-containing protein) is modified by a thiol-containing extender, comprising a reactive group capable of forming an irreversible covalent bond with the thiol group on the target molecule, a portion having intrinsic affinity for the target molecule, and a thiol group. The complex formed between the target molecule and the thiol-containing extender is then used to screen a library of disulfide-containing monophores to identify a library member that has the highest intrinsic binding affinity for a second binding site on the target molecule. LG = [ligand] leaving group; PG = protecting group; R = reactive group. - -

Paragraph [0034] has been replaced by the following new paragraph:

- - A "ligand" as defined herein is an entity which has an intrinsic binding affinity for the target. The ligand can be a molecule, or a portion of a molecule which binds the target. The ligands are typically small organic molecules which have an intrinsic binding affinity for the target molecule, but may also be other sequence-specific binding molecules, such as peptides (D- , L- or a mixture of D- and L-), peptidomimetics, complex carbohydrates or other oligomers of individual units or monomers which bind specifically to the target. The term "monophore" is used herein [interchangeably with the term "ligand" and refers] to refer to a monomeric unit of a ligand. The term "diaphore" denotes two monophores covalently linked to each other.[form a unit that has a higher affinity for the target because of the two constituent monophore units or ligands binding to two separate but nearby sites on the target. The binding affinity of a diaphore that is higher than the product of the affinities of the individual components is referred to as "avidity."] The term diaphore is used irrespective of whether the unit is covalently bound to the target or

existing separately after its release from the target. The term also includes various derivatives and modifications that are introduced in order to enhance binding to the target. The binding affinity of a diaphore that is higher than the product of the affinities of the individual components is referred to as "avidity." - -

Paragraph [0075] has been amended as follows:

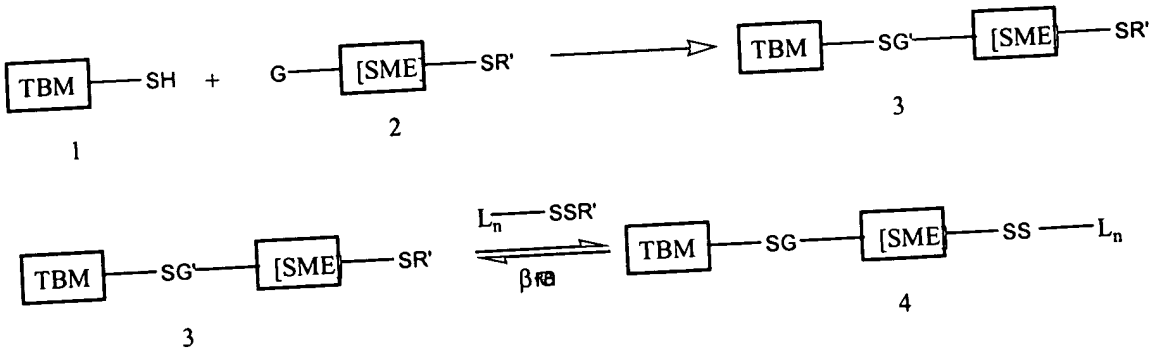
- - It is also preferred that the residue to be mutated to cysteine, or another thiol-containing amino acid residue, not participate in hydrogen-bonding with backbone atoms or, that at most, it interacts with the backbone through only one hydrogen bond. Wild-type residues where the side-chain participates in multiple (>1) hydrogen bonds with other side-chains are also less preferred. Variants for which all standard rotamers (chi1 angle of –60°, [60°] 120°, or 180°) can introduce unfavorable steric contacts with the N, CA, C, O, or CB atoms of any other residue are also less preferred. Unfavorable contacts are defined as interatomic distances that are less than 80% of the sum of the van der Waals radii of the participating atoms. - -

Paragraph [0080] has been amended as follows:

- - Preferred TBM's are proteins and the preferred nucleophiles on the TBM's suitable for forming an irreversible TBM-SME complex include -SH, -OH, $-NH_2$ and –COOH usually arising from side chains of cys, ser or thr, lys and asp or glu respectively. TBM's may be modified (e.g. mutants or derivatives) to contain these nucleophiles or may contain them naturally. For example, cysteine proteases (e.g. Caspases, especially 1, 3, 8 and 9; Cathesepins, especially S and K etc.) and [phosphotases] phosphatases (e.g. PTPα, PTP1B, LAR, SHP1,2, PTPβ and CD45) are examples of suitable proteins containing naturally occurring cysteine thiol nucleophiles. Derivatizing such TBM's with a SME to produce a static TBM-SME complex and its reaction with a library member is illustrated below. - -

The reaction chart on top of page 36 has been amended as follows:

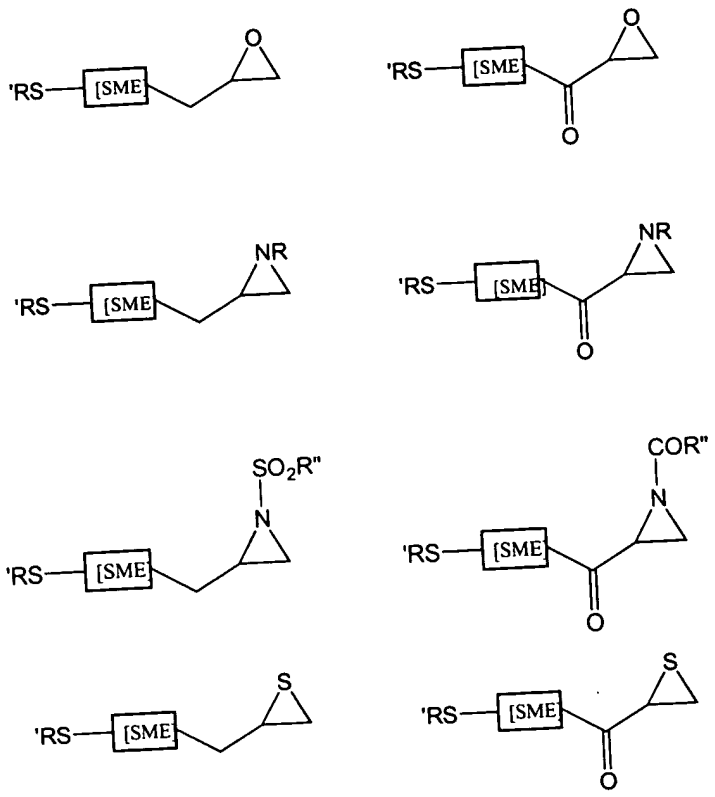
- -



- -

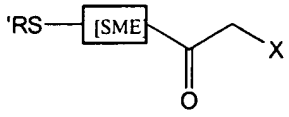
The structures at the bottom of page 37 and at the top of page 38 have been amended as follows:

- -

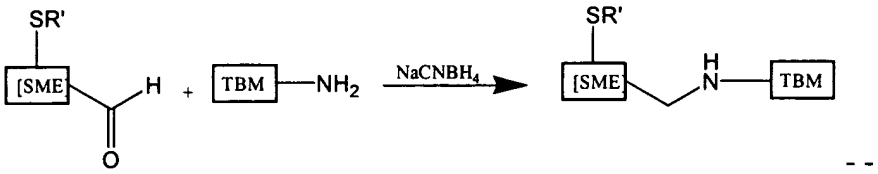


- -

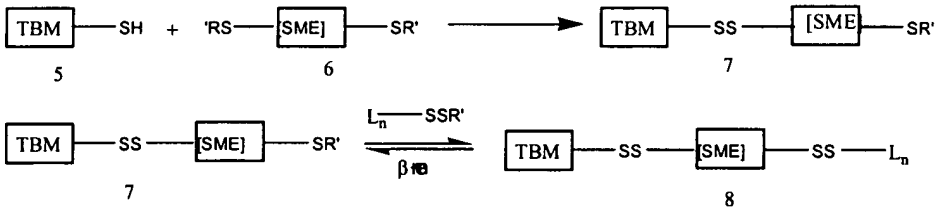
The structure following paragraph [0085] on page 38 has been amended as follows: - -



The chart following paragraph [0088] on page 39 has been amended as follows: - -

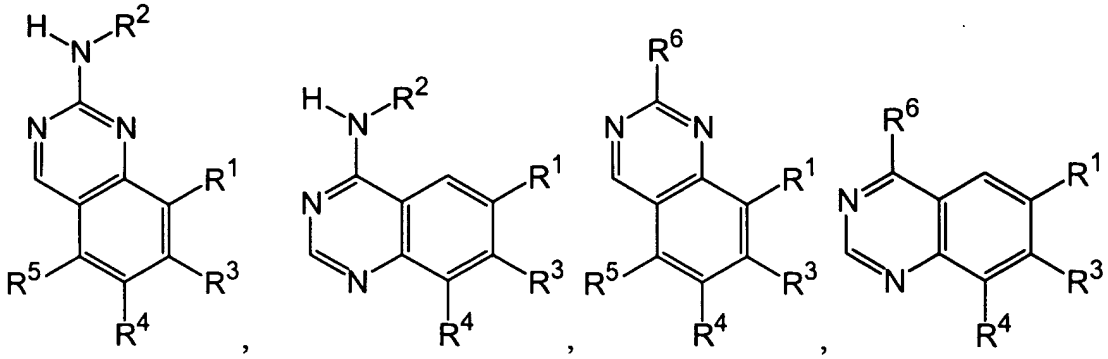


The chart on the top of page 41 has been amended as follows: - -

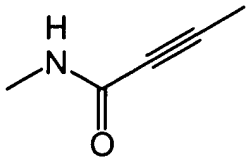
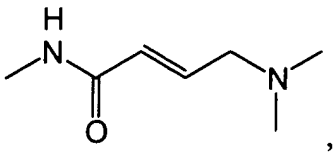
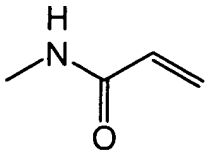


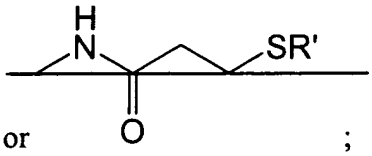
The first paragraph on top of page 45 has been amended as follows: - -

SME's are often customized for a particular TBM or family of TBM's. For example quinazoline derivatives are capable of forming static or dynamic extenders with the EGF receptor or an "RD" kinase. In the case of the EGF receptor, cys 773 is a suitable nucleophile for either a static or dynamic quinazoline extender as shown below;

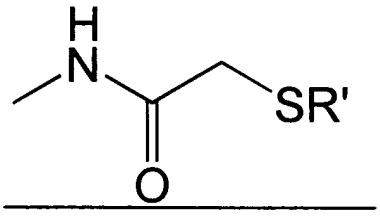


where R^1 is linked to cys 773 through a Michael acceptor or disulfide,

R^1 is selected from  ,  , 



or ;



R^2 is $-(CH_2)_n$-SR' and $-C(=O)-(CH_2)_n$-SR';

R^3, R^4 and R^5 are $-O-(CH_2)_n$-SR' and $-(CH_2)_n$-SR';

R^6 are; $-(CH_2)_n$-SR'; where n is 1, 2, or 3 and

R' is H, a disulfide or a thiol protecting group. - -

Paragraph [0104] has been amended as follows:

- - Phosphotyrosine (P-tyr), phosphoserine (P-ser) and phoshpothreonine (P-thr) mimetics or surrogates may be used as extenders in the present invention to identify fragments that interact with subsites nearby to improve specificity or affinity for a target [phosphotase] phosphatase. Thus extended tethering using known substrates or inhibitors as "anchors" to find nearby fragments by standard covalent tethering with the extender is one preferred embodiment of the instant invention. - -

Paragraph [0105] has been amended as follows:

- - Phosphotyrosine (P-tyr) mimetics are examples of SME's that may be customized for [phosphotases] phosphatases like PTP-1B, LAR etc. Known PTP-1B P-tyr mimetics derivitized with mercapto-propanoic acid and/or cysteamine or the protected forms thereof, shown below, bind to the active site of a PTP-1B cys mutant. - -